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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SMITH, CAROLYN L	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 10/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,982	HACOHEN ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sh t with the c rrespondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-9 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-9,and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' election of Group I (claims 1, 5-9, 51, and 55), election of Specie A (method involving a nucleic acid), and cancellation of claims 2-4, 10-50, and 52-58, filed 8/20/2003, are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title is directed to a response of dendritic cells to a diverse set of pathogens, whereas in contrast the elected claims are specifically directed to methods of identifying a pathogen and diagnosing infection in a mammal.

Claims herein under examination are 1, 5-9, and 51.

Claim Rejections – 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the

amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of the skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF SCOPE OF ENABLEMENT

Claims 1, 5-9, and 51 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for identifying certain organisms, does not reasonably provide enablement for identification of any type of pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The preamble of claims 1, 5, 9, and 51 refer to identifying a pathogen or diagnosing infection from a pathogen. However, the specification only provides information based on a Gram-negative bacterial species (*E. coli*); its cell wall component, lipopolysaccharide (LPS); a fungus (*C. albicans*); its yeast cell wall-derived mannan; an RNA virus (influenza A); and its double-stranded RNA (dsRNA). A significant additional amount of experimentation would be necessary to determine whether other pathogens could be identified in a similar manner.

Also, claims 6-8 mention stimulus-specific and stimulus-responsive gene probes. The specification mentions a wide variety of potential stimuli ranging from bacteria, fungi, viruses, or components thereof; physical, chemical, or electrical stimuli; and

inorganic or organic chemicals (page 5, first paragraph). Adequate working examples and direction was presented for the bacterium, fungus, and virus (as stated in the previous paragraph); however, adequate information regarding other types of stimuli was not presented to sufficiently enable the entire breadth of these claims.

LACK OF ENABLEMENT

Claims 1, 5-9, and 51 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention.

Claims 1, 5, 9, and 51 are directed to identifying a pathogen by noting stimulus-specific genes that are specific to a particular pathogen. It seems this very broad assertion cannot stand based solely on the three types of pathogens tested. For example, this application lists figures where some genes showed specificity after stimulus from either *E. coli*, *C. albicans*, or influenza. It is well known that many types of pathogens exist in the world, some of which are known and some of which are yet undiscovered. Generically stating that the genes in the figures are specific to one of these particular pathogens does not appear to be a valid statement when it is impossible to know if these genes do in fact exhibit a stimulus response to pathogens not tested in this study.

A similar issue arises in claims 6-8 where a hybridized probe is asserted to be indicative of infection. A probe that was originally associated with a stimulus may or may not provide actually be associated with an infection that the stimulus might cause. To determine the validity of these claims, each instance must be separately examined to

determine the underlying factors in any particular infection. Therefore, it appears that undue experimentation would be required for these broad claims as currently written.

The methods in this application claim to identify pathogens or diagnose infection. However, none of the method steps in these claims mentions a comparison to a control which is paramount to equating a gene to a particular association during gene expression analysis.

Finally, a gene resulting in modified expression after implementing a stimulus is, in fact, associated with and indicates stimulation has occurred. However, one of skill in the art cannot automatically conclude that this modification in expression also indicates infection has occurred without further experimentation to verify this assertion.

Claims Rejected Under 35 U.S.C. § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 8 recites the word "common" which is vague and indefinite. It is unclear what the metes and bounds are for this term. Clarification of this issue via clearer claim wording is requested.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-9, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cummings et al. (Genomics, Vol. 6, No. 5, Sept-Oct 2000, pages 513-525) in view of Hashimoto et al. (Blood, Vol. 96, No. 6, September 2000) and Cirillo (WO 02/08418).

Cummings et al. describe methods of using host gene microarrays to explore gene level expressions that follow infection of a microbial pathogen (abstract). Cummings et al. describe host profiling as a way to identify gene expression signatures unique for each pathogen to be used as a tool for diagnosis, prognosis, and clinical management of infectious disease (abstract). The instant specification states a "stimulus" includes bacteria, fungi, viruses, or components thereof (page 5, first paragraph). Therefore, the

unique gene expression signature due to pathogen infection mentioned by Cummings et al. is reasonably interpreted to include "stimulus-specific" genes as stated in claim 1. Cummings et al. describe that gene expression profiling of host-pathogen interactions are emerging in the science field (page 514, col. 1, first paragraph). Cummings et al. describe examining infected cultured cells (page 520, col. 1, fifth paragraph) which is reasonably interpreted as cells that have come into contact with a pathogen. Cummings et al. describe preparing and purifying mRNA from eukaryotic cells (including humans, a type of mammal) to be used in hybridization experiments with microarrays (Figure 1; page 514, col. 2, second paragraph; and page 515, col. 1, first paragraph and col. 2, second paragraph). Cummings et al. describe isolating and labeling RNA from microbial samples as well (page 518, col.2, third paragraph). Cummings et al. describe labeling mRNA in the microarray methodology (page 515, col. 1, first paragraph). Cummings et al. describe performing a cross-species comparison of many different pathogens (page 517, col. 1, second paragraph). Cummings et al. describe monitoring gene expression in M. tuberculosis, a pathogen, while it infects cultured monocytes (page 518, col. 1, second paragraph). Cummings et al. describe genes that are specifically expressed during infection (page 518, col.2, third paragraph). Cummings et al. describe using arrays to monitor gene expression in primary human fibroblasts infected with human CMV and noting fourfold differences between infected and uninfected human genes (page 520, col. 2, first paragraph). Cummings et al. describe examining HIV-1 infection in CD4-positive T cells and noting differential expression in 20 human genes (page 520, col. 2, second paragraph). Cummings et al. describe examining response to host cells to infection with bacterial pathogens (page 520, col. 2, third paragraph). Cummings et al. describe

examining the response of human (a type of mammal) promyelocytic cells to *L. monocytogenes* infection (page 520, col. 2, fourth paragraph). It is noted in Webster's NewWorld Medical Dictionary that promyelocytic cells are immature myelocytes which can be nerve cells of gray matter of the brain or spinal cord. It is also noted in this dictionary that dendritic cells include nerve cells. Cummings et al. describe comparison of gene expression profiling data from human monocytes infected by different strains of virus (page 521, col. 1, third paragraph) which is interpreted to be an analysis of gene profiles relative to other reference profiles to identify stimulus-specific genes for a particular pathogen, as stated in claim 5. Cummings et al. describe microarrays used in measuring responses of cultured cells to distinct external stimuli (page 521, col. 2, second paragraph). Cummings et al. describe measuring gene expression in leukocytes to find signatures diagnostic of infection by specific pathogens (page 521, col. 2, third paragraph). Cummings et al. describe using these host gene expression signatures as diagnostic markers (or probes) of infection (page 521, col. 2, fourth paragraph) which is reasonably interpreted to be stimulus-responsive gene probes, as stated in claims 6, 7, and 8. Cummings et al. describe identification of gene expression profiles common to many different pathogens (page 522, col. 1, second paragraph) which is reasonably interpreted to include common stimulus-responsive gene probes, as stated in claim 8.

Cummings et al. does not specifically describe dendritic or immature dendritic cells (claims 1, 5, 6, 9, and 51) or contacting mRNA with probes (although Cummings does mention diagnostic markers which infers this probe activity).

Hashimoto et al. describe comparing and identifying genes specifically expressed in human mature or immature dendritic cells after being stimulated with

lipopolysaccharide (LPS) (title and abstract). The instant specification states LPS as being a stimulus in a particular embodiment (page 5, first paragraph).

Cirillo describes methods of detecting *Legionella pneumonophila* bacteria in samples (abstract). Cirillo describes a method of diagnosis of Legionnaires disease in a subject by obtaining RNA from a sample suspected of being infected with *L. pneumophilia*, and contacting the RNA with a specific nucleic acid molecule (probe) which will hybridize to a particular gene or mRNA to be able to detect *L. pneumonophilia* (page 7, second paragraph). Cirillo describes genes specific for L. *pneumonophilia* and their mRNA which can be used to detect this bacteria (page 23, lines 30-33). Cirillo describes using RNA probes with specificity that will hybridize and detect this gene (page 23, line 34 to page 25, line 6). Cirillo describes activating THP-1 (monocyte cells) with LPS and adding bacteria to the cells (page 48, lines 11-13). Cirillo describes bacteria interacting with HEp-2 (epithelial cells) (page 32, lines 16-17).

Cummings et al. state the interaction between a microbial pathogen and a host is the underlying basis of infectious disease (page 513, col. 1, first paragraph). Cummings et al. also state that understanding the details of this interaction will help us identify virulence-associated microbial genes and host defense strategies and their regulated (page 513, col. 1, first paragraph). Cummings et al. state this information will guide the design of a new generation of medical tools (page 513, col. 1, first paragraph). Cummings et al. state explaining life at a molecular level is slow because gene function understanding lags behind and that high throughput methods are required (page 513, col. 1, second paragraph to col. 2, first paragraph). Cummings et al. state microarray-based approaches hold exceptional promise and will make substantial contributions for studying infectious

disease (page 513, col. 2, third paragraph). Cummings et al. state the goals of functional genomics and microarray technology in infectious diseases will require additional technology, extensive data collection, and sophisticated computational tools (col. 522, col. 1, fourth paragraph). As Cummings et al. state the goals of identifying and diagnosing host-pathogen interactions (page 522, col. 1, fourth paragraph), one of ordinary skill in the art would have been motivated to perform such microarray technology on cells, genes, and pathogens already known to be specific for a particular pathogen (abstract). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use the dendritic cells, such as those noted by Hashimoto et al., and the probes as stated by Cirillo, in the microarray technology suggested by Cummings et al. in order to help further identify genes unique for each pathogen. One would have a reasonable expectation of success since specificity was already determined in genes involving cells stimulated by LPS (Hashimoto et al. and Cirillo) and a pathogen (Hashimoto et al.). Thus, Cummings et al., in view of Hashimoto et al. and Cirillo motivate the instant invention.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61

(November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

October 27, 2003

ARDIN H. MARSCHEL